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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,834	01/25/2002	Mark J. Ratain	ARCD:358US	1557

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,834	RATAIN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-108* is/are pending in the application.

4a) Of the above claim(s) *19-40, 42, 44-65, 67, 72-93, 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,41,43,66,68-71 and 94-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/5/03, 7/7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-100 in the reply filed on July 19, 2004 is acknowledged. Further, Applicant elected the species of epirubicin. The claims readable on the elected species are claims 1-18, 41, 43, 66, 68-71 and 94-100.

Information Disclosure Statement

2. The information disclosure statement filed July 7, 2003 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. Specifically, the IDS does not include a statement regarding the relevance of the non-English document EP 0919244.

Claim Objections

3. Claim 1 is objected to because of the following informalities:

Claim 1 is objected to because "UGTB7" should read "UGT**2**B7."

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 41, 43, 66, 68-71 and 94-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining

the dose of morphine to administer to a patient wherein the method comprises obtaining a sample nucleic acid from a patient, analyzing the sample nucleic acid directly for the presence of a polymorphism in the UGT2B7 gene, detecting the presence or absence of a T or C polymorphism at position -161 of the UGT2B7 gene or the presence of a TC or AT polymorphism at positions 801-802 of the UGT2B7 gene and determining the appropriate dose of morphine to administer to the patient based on the presence or absence of one of said polymorphisms and while enabling for general methods of assaying for UGT2B7 glucoronidation of epirubicin, does not reasonably provide enablement for all methods for determining a dose of any UGT2B7-glucoronidated drug by assaying for the level of UGT2B7 activity, assaying for the activity of UGT2B7 or assaying for the presence of any polymorphism in the UGT2B7 gene or other unstated gene as a means for determining the dose of any UGT2B7-glucoronidated drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for determining the dose of any UGT2B7-glucoronidated drug wherein the methods comprise determining the level or activity of UGT2B7 and determining the dose of the drug based on the activity or level of UGT2B7. The claims include methods in which UTG2B7 is directly assayed for enzyme activity, for the level of protein or mRNA, or for the presence of any first polymorphism associated with UTG2B7 activity or for any second polymorphism linked to said first polymorphism. The claims further encompass methods for evaluating the risk of toxicity of any UGT2B7-glucoronidated drug by directly or indirectly determining the nucleotide sequence at position –161 of the UGT2B7 gene; methods for screening for glucoronidation activity by identifying any polymorphism that correlates with glucoronidation activity; and methods for predicting the degree of an epirubicin-induced toxicity in a cancer patient by directly or indirectly determining the nucleotide sequence at position –161 of the UGT2B7 gene.

The specification teaches that UGT's catalyze the glucoronidation of distinct substrates. The specification also teaches that there is considerable variability between individual's with respect to their glucoronidation activities and suggests that the presence of polymorphisms in UGT genes may influence glucoronidation activity. In Table 1, the specification discloses 15 polymorphisms in the UGT2B7 gene. Two additional polymorphisms are disclosed in Table 6. The specification (see Example 11) also teaches that the –161 promoter polymorphism is in complete linkage disequilibrium (LD) with the +801/+802 polymorphisms, which lead to a His > Tyr mutation at amino acid position 268. Further, the specification (see, e.g., page 110) teaches that the T/T –

161 genotype is associated with increased glucoronidation of morphine to M6G and M3G as compared to the C/C –161 genotype. Thereby, the specification has established an association between the –161 T/C polymorphism and glucoronidation of morphine. However, with respect to the cancer therapeutic epirubicin, the specification (page 101) teaches that "Differences in epirubicin glucoronidation between UGT2B7(H) and UGT2B7(Y) variants were not observed." Accordingly, the specification has not established a correlation between glucoronidation of epirubicin and any particular polymorphism in the UGT2B7 gene or changes in the level or activity of UGT2B7.

The specification is enabling only for methods in which a dosage of morphine is selected for a patient based on the presence or absence of a T or a C at position –161 of the UGT2B7 gene or the presence or absence of TC or AT at positions +801/+802 of the UGT2B7 for the following reasons:

The results obtained with morphine glucoronidation cannot be extrapolated to other UGT2B7-glucoronidated drugs because the activity of UGT2B7 variants differs with respect to the drug and with respect to the particular UGT2B7 variant. This finding is highlighted by the teachings in the specification that the UGT2B7(H) and UGT2B7(Y) variants (i.e., the polymorphisms at positions –161 and at +801/+802) do not show differences in their ability to glucoronidate epirubicin, while these variants do appear to show differences in their ability to glucoronidate morphine.

The ability to determine an association between UGT2B7 levels/activity and the presence of specific polymorphisms is highly unpredictable. Again, the effect of a

polymorphism appears to be substrate-dependent. Further, there is no clear association between any particular polymorphism and glucoronidation levels or activity. The specification does not teach any specific polymorphisms which alter the level of UGT2B7 protein or mRNA. Nor, does the specification teach any polymorphism which is associated with an increase or decrease of UGT activity with respect to all UGT2B7 substrates. The specification teaches only one set of polymorphisms – i.e., the –161 and +801/+802 polymorphisms – which are associated with the degree of glucoronidation of morphine. No additional polymorphisms associated with morphine glucoronidation have been disclosed and no polymorphisms are disclosed in the specification which are clearly associated with any other UGT2B7 substrates.

With respect to epirubicin in particular, no working examples are provided in the specification in which a dosage of epirubicin is selected based on differences in the level of UGT2B7 mRNA or protein, differences in the level of UGT2B7 activity, or the presence or absence of a polymorphism. The specification has not established that individual's possess different levels of UGT2B7 mRNA or proteins or have different UGT2B7 activity levels which clearly correlate with the efficiency of glucoronidation of epirubicin. The specification does not teach how to determine the appropriate dosage of epirubicin to be administered to a patient based on the level or activity of UGT2B7 because the specification has not established that UGT2B7 levels and activities vary between patients and that these changes alter the level of epirubicin glucoronidation. Thereby, the specification does not provide sufficient guidance as to how to determine

the dosage of epirubicin by assaying for the presence of a polymorphism or by assaying for epirubicin mRNA or protein levels or enzyme activity.

The unpredictability of determining an association between UGT2B7 level/activity and the occurrence of a polymorphism is supported by the teachings in the art. For example, Bhasker (Pharmacogenetics (2000) 10: 679-685) teaches that there was no observed differences between the rates of glucoronidation of androsterone, menthenol and morphine with respect to the UGT2B7(H) and UGT2B7(Y) variants (see page 683). Bhasker (page 684) concludes that "His268Tyr substitution minimally influences enzyme activity, and the clearances of drugs and other compounds metabolized by UGT2B7 would not be expected to vary substantially with genotype. However, a significant effect on specific substrates cannot be discounted." Further, Bhasker (page 684) emphasizes that "Although the UGT2B7 polymorphism described here may not be associated with altered enzyme activity, the results highlight the need to consider racial variability in assessing the consequences of UGT polymorphisms."

Additionally, Innocenti et al (of which the present inventors are co-authors; Drug Metabolism and Disposition. 2001. 29: 686-692; see abstract) states that "The reported tyrosine to histidine polymorphism in UGT2B7 does not alter the formation rate of epirubicin glucoronide, and *undiscovered genetic polymorphisms in UGT2B7 might change the metabolic fate of this important anticancer drug"* (emphasis added). Accordingly, at the time the invention was made, and as of 2001, an association between epirubicin glucoronidation and the presence of any particular polymorphism in the UGT2B7 gene had not yet been discovered.

Additionally, Toide (Drug Metabolism and Disposition (2002) 30: 613-615) supports the finding that it is unpredictable as to whether UGT2B7 mRNA levels are associated with changes in enzyme activity. Toide (see abstract) reports that "A novel point mutation (-253G to A) found in this study did not affect the level of UGT2B7 mRNA in subjects." Toide (page 615) found that "interindividual variation in the UGT2B7 enzyme activity occurred by the variation in the amounts of HNF-1a mRNA" rather than as a result of variation in the amount of UGT2B7 mRNA.

In view of the high level of unpredictability in the art as set forth above, an association between a UGT2B7 polymorphism or UGT2B7 activity or protein or mRNA levels can only be established through extensive experimentation. Such experimentation requires analyzing the UGT2B7 gene for the presence of a known or unknown polymorphism, determining whether the polymorphism is directly associated with a change in the level or activity of glucoronidation of a specific UGT2B7 substrate or by determining whether the polymorphism is indirectly associated with UGT2B7 levels or activity by screening for the presence of the polymorphism in a population showing a difference in their ability to glucoronidate specific substrates, and trying to determine which, if any, of the identified polymorphisms are directly or indirectly associated with a change in UGT2B7 levels or glucoronidation of specific substrates. There is no means to predict a priori which of the multitude of possible polymorphisms in UGT2B7 genes or genes linked thereto would be associated with any one or more of the various UGT2B7 substrates. Accordingly, such, random, trial-by-error experimentation is considered to be undue.

Further, it is noted that the claims are written in a manner such that they do not require the direct analysis of any particular polymorphism. Rather, the claims encompass indirectly inferring the presence of a polymorphism or the level of activity of UGT2B7 by assaying for the presence of some unstated polymorphism that may be linked to whatever degree to some other stated or unstated polymorphism, by performing some unspecified activity assay or by determining the level of some unspecified mRNA or protein. However, the specification has not taught a representative number of polymorphisms, activity assays or proteins or mRNAs which can be analyzed to predictably determine the level of UGT2B7 activity to a specific substrate. The specification has taught only an association between the occurrence of the –161 polymorphism and the +801/+802 polymorphisms. No additional polymorphisms in complete linkage disequilibrium with –161 or +801/+802 have been identified. Nor has the specification disclosed any additional UGT2B7 polymorphisms in linkage disequilibrium with other UGT2B7 polymorphisms or polymorphisms present in other unspecified genes. No specific guidance has been provided in the specification as to what would be the identity of other polymorphism in linkage disequilibrium with an a polymorphism correlated with glucoronidation activity or the identity of other mRNAs or proteins which could be analyzed to provide information on the level or activity of UGT2B7.

The claims also include methods of determining a dose of a UGT2B7-glucoronidated drug by assaying for glucoronidation activity in general. However, as discussed above, it is expected that variants of UGT2B7 may have different activities

with respect to different substrates. Thereby, assaying an individual's UGT2B7 activity in general will not provide an accurate reflection of that individual's capacity to glucoronidate a specific UGT2B7 substrate. To determine an appropriate dosage of a UGT2B7-glucoronidated drug requires determining the level of UGT2B7 activity in an assay using that specific drug as a substrate.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation" (*In re Wright* 990 F.2d 1557, 1561). *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement." In the instant case, the scope of the claims does not bear a reasonable correlation to the scope of enablement because the specification has established an association only between one specific UGT2B7 substrate, i.e. morphine, and one specific set of polymorphisms, i.e., the –161 and +801/802 polymorphisms. The specification does not teach a correlation between a representative number of substrates and polymorphisms or UGT2B7 variants having increased or decreased expression levels or activities. In view of the high level of

unpredictability in the art and the lack of specific guidance provided by the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

5. Claims 10, 43, 66, 68-71, and 94-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite and confusing over the recitation of "identification of a second thymine," "identification of a second cytosine," and "identification of a residue different than the residue in the first promoter" because the claim does not previously refer to a first thymine, cytosine or residue in the promoter. Thereby, it is unclear as to how claim 10 is intended to be further limiting from claim 3 and it is unclear as to what would constitute a residue that is different from the residue in the first promoter.

Claim 43 and 66 are indefinite over the recitation of "determining the activity of UGT2B7 in a patient according to the method" because the phrase "the method" lacks proper antecedent basis. The claim does not specifically recite any method steps for determining UGT2B7 activity and thereby it is unclear as to what is intended to be encompassed by "the method." Additionally, claims 43 and 66 are indefinite over the recitation of "administering a dose of the drug to administer to the patient" because it is not clear as to what is intended to be meant by this phrase.

Claims 68-71 are indefinite. The claims are drawn to a method for evaluating the risk for toxicity from a UGT2B7-glucoronidated drug in a patient. The claims recite a final step

of determining the nucleotide sequence at position –161 in one UGT2B7 gene. However, the claims do not clarify how the step of determining a nucleotide sequence results in the evaluation of the risk of toxicity. There is no nexus between the preamble of the claim and the final process step. Thereby, it is unclear as to whether the method is intended to be one for evaluating the risk for toxicity from a UGT2B7-glucoronidated drug in a patient or one for determining the nucleotide sequence at position –161 in one UGT2B7 gene.

Similarly, claims 94-98 are indefinite because the claims are drawn to methods for screening an individual for glucoronidation activity, yet recite a final step of identifying the nucleotide sequence of a polymorphism. The claims do not recite a clear nexus between identifying the nucleotide sequence of a polymorphism and determining glucoronidation activity. It is thereby unclear as to whether the claims include methods which merely determine a UGT2B7 nucleotide sequence, or whether the claims are intended to encompass methods of screening for glucoronidation activity.

Claim 99 is indefinite. The claim is drawn to a method for prescribing a dose of a UGT2B7-glucoronidated drug. However, the final step is one for determining the level of UGT2B7 activity. The claim does not recite a clear nexus between the preamble and final process step and it is unclear as to how determining the level of UGT2B7 results in the prescription of a dose of a UGT2B7-glucoronidated drug.

Claim 100 is indefinite. The claim is drawn to a method for predicting the degree of an epirubicin-induced toxicity. However, the claim recites a final step of determining the

nucleotide sequence at position –161. The claim does not recite a clear nexus between the preamble and the final process step and it is unclear as to how determining the nucleotide sequence at position –161 accomplishes the objective set forth in the preamble of the claim of predicting the degree of epirubicin-induced toxicity. Thereby, it is unclear as to whether the claim is intended to be limited to methods for predicting the degree of an epirubicin-induced toxicity or methods for determining the nucleotide sequence at position

–161.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Carla Myers

September 27, 2004

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER